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Soluble Fas Ligand in Natural Killer Cell Lymphoma

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We measured serum soluble Fas ligand (sFasL) in a patient with natural killer cell lymphoma, and investigated relationship between sFasL and liver dysfunction. An elevated level of sFasL was decreased after local radiation therapy, and liver function improved. When lymphoma relapsed, liver dysfunction reappeared and the level of sFasL increased parallelly. Lymphoma cells expressed mRNA of FasL. This suggested that this liver dysfunction was induced by some remote effectors, and sFasL was one of candidates of these effectors. Am. J. Hematol. 62:253–255, 1999. © 1999 Wiley-Liss, Inc.

Key words: NK cell lymphoma; soluble Fas ligand; liver dysfunction; Fas; remote effect

INTRODUCTION

Natural killer (NK) cell lymphoma usually originates from the nasal cavity, and its prognosis is very poor because of chemotherapy resistance and complications, including liver dysfunction. As the liver dysfunction progresses or improves with the progression or reduction of their original lymphomas, it may be induced by some lymphoma-derived factors. Fas Ligand (FasL) is produced in NK cells and is one candidate of these factors. In this report, we measured soluble FasL (sFasL) in stage II NK cell lymphoma treated with only radiation therapy, and investigated its relationship to liver dysfunction and lymphoma.

CASE REPORT

A 41-year-old male was admitted because of fever and cervical lymph node swelling. He was well until April 1997 when he felt left cervical lymphadenopathy. He visited the local hospital where he was diagnosed as malignant lymphoma. He was referred to our center on June 25. He had low grade fever, left cervical and supraclaviclar lymph node swelling. Biochemical examination showed elevation of GOT, GPT, and LDH, and antibodies to HBs, HBe, HBc, and HCV were positive. However, HBs and HBe antigens were negative, and RNA of HCV was also negative. Biopsy specimen of left supraclaviclar lymph node showed diffuse lymphoma. Lymphoma cells were CD2-positive, CD3-negative, CD7-negative, and CD56-positive. He was diagnosed as Stage II by galium sincigraphy and computed tomography, because of localized disease in left cervical and supraclaviclar region. As NK cell lymphoma is chemotherapy-resistant, we chose radiation therapy—local and mini-mantle radiation. After radiation of 42.5 Gy, left cervical and supraclaviclar tumor had disappeared, and radiation therapy was discontinued because of myelosuppression. In early August fever, liver dysfunction and proteinuria reappeared, although relapse of lymphoma was not detected. He had dyspnea and right pleural effusion rapidly increased. There were many CD56-positive cells in this pleural effusion. He expired on August 8.

We analysed expression of FasL mRNA in the cervical lymph node, lymphoma cells in pleural effusion and peripheral blood mononuclear cells (PBMNCs) by using a

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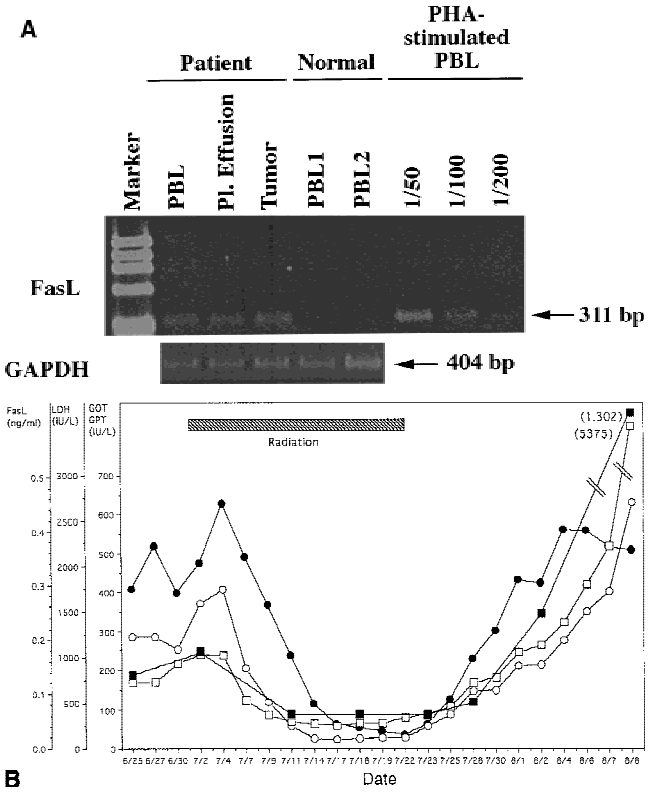

Fig. 1. (A) Expression of mRNA of Fas ligand in lymphoma tissue, mononuclear cells in patient periferal blood at relapse and lymphoma cells in pleural effusion. (B) Clinical course of GOT (○), GPT (●), LDH (□), and sFasL (■). GOT, GPT, and LDH was normalized with radiation therapy and sFasL also decreased. After radiation, sFasL increased again, and liver dysfunction progressed parallelly.

SuperScript preamplification system (BRL) and Ex-Taq DNA polymerase (TaKaRa Shuzo, Kyoto, Japan) as described [1]. However, healthy donor PBMNCs without stimulation did not express mRNA of FasL (Fig. 1A). We also measured the level of sFasL in serum by using sFasL ELISA kit (Medical and Biological Lab. Nagoya, Japan). The sensitivity of this assay is 0.1 ng/ml in serum, and concentration of sFasL in normal serum is less than 0.1 ng/ml. His clinical course as well as biochemistry data was reviewed. On admission, he had liver dysfunction and increased level of GOT, GPT, and LDH. Before irradiation, GOT, GPT, and LDH were elevated, and sFasL also elevated parallelly. After the initiation of irradiation, tumor became smaller, and levels of GOT, GPT, LDH, and sFasL were decreased without any other treatment. In July, liver dysfunction disappeared and GOT, GPT, LDH, and sFasL had been normalized. After the termination of irradiation, the levels of GOT, GPT, LDH, and sFasL were increased again, and lymphoma cells invaded the pleural cavity causing effusion (Fig. 1B).

DISCUSSION

FasL, a cell surface molecule belonging to the tumor necrosis factor family, binds to its receptor Fas, thereby inducing apoptosis of Fas-bearing cells [2–4]. FasL is expressed in NK cells [3]. FasL also exists as a soluble form in serum [5]. Tanaka et al reported that serum FasL level in NK cell lymphoma is higher than that in other disease [6]. On the other hand, Fas is expressed not only in lymphocytes but also in liver [7]. Anti-mouse Fas antibodies (Jo2) induce fulminant hepatitis in vivo [8]. These facts suggest that abnormal activation of Fas system has pathological effects in hepatic disease.

In this case, lymphoma was localized in left cervical region. He had elevated level of sFasL with liver dysfunction before irradiation. Lymphoma cells in the cervical lymph node expressed mRNA of FasL. Radiation field was left cervical region and a part of mantle field; thus, this radiation did not affect his liver directly. Liver function improved with mass reduction of cervical lymphoma. Serum sFasL level was normalized. After interruption of radiation therapy, lymphoma regrew, and liver function also deteriorated. Serum sFasL level gradually elevated. The grade of liver function was parallel with serum FasL level. Elevation of serum sFasL was thought to be induced by increase of lymphoma cells. Thus, it is suggested that in NK cell lymphoma, some tumor-derived factor induced liver dysfunction as remote effect and sFasL was a candidate of these factors. We think that FasL in serum may be one tumor marker of NK cell lymphoma. In this case, complicated multiorgan dysfunction made treatment of lymphoma difficult with drug resistance. If the Fas/FasL system is a major part of this multiorgan dysfunction in NK cell lymphoma, it may be effective to combine normal chemotherapy with Fas/FasL system inhibitors as suggested in Sato's report [9].

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